REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Claim 1 has been amended. Reconsideration is respectfully requested in light of the claim amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 103(a)

Claim 1 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Chamberlain et al. (1998). The Examiner suggests that this reference teaches administration of methotrexate to patients with leptomeningeal metastases presenting with radiculopathy, wherein the dose of methotrexate is administered intraventricularly and is a dose of 2 mg daily (total dose of 40 mg; approximately 0.029 mg/kg/day based on a 70 kg individual or 0.033 mg/kg/day based on a 60 kg individual). The Examiner acknowledges that this reference fails to teach intrathecal administration of methotrexate. The Examiner suggests that a medical dictionary teaches that intraventricular administration is administration either within the subarachnoid space or the subdural space. The Examiner suggests it is unknown whether the injection subdurally is into the back or the back of

the head, and as such overlaps with the claimed invention. Further, the Examiner suggests that the dose taught by Chamberlain et al. is encompassed by the dose range claimed. Therefore, the Examiner suggests that the invention is *prima facie* obvious over Chamberlain et al. Applicants respectfully disagree with the Examiner's conclusions regarding this reference.

Claim 1 recites that local administration into the back of the animal is intrathecal administration, as is defined in the specification as filed at page 5, and acknowledged by the Examiner. Also as acknowledged by the Examiner, Chamberlain et al. (1998) disclose only the intraventricular administration of methotrexate. The Examiner, however, erroneously suggests that the teaching of Chamberlain is a dose of methotrexate of 2 mg/kg. The dose actually taught is 2 mg daily, 20 drug administrations for a total dose of 40 mg. On a daily basis this is 0.029 mg/kg/day for a 70 kg individual or 0.033 mg/kg/day for a 60 kg individual, doses well below the Examiner's claimed dose of 2 mg/kg/day. Applicants again respectfully point out the Examiner is absolutely mistaken in the assertion that intraventricular administration of a drug is the same as intrathecal

administration. It is general principle of human physiology and pharmacokinetics that intraventricular administration will not produce a local concentration of active drug in the spinal cord area that is anywhere near the same concentration as would be achieved with intrathecal administration. This is because, as taught in basic human anatomy and physiology texts (e.g., *Human Anatomy and Physiology*, Second Edition, Elaine N. Marieb (editor), Benjamin Cummings Publishing: Redwood City, CA, pages 404-405, starting at the second column on page 404) the circulation of cerebrospinal fluid through the brain ventricles is designed such that only some of the cerebrospinal fluid from the ventricles circulates into the central canal of the spinal cord. As is taught in this text, "most enters the subarachnoid space" (see page 404, second column, line 3-4 of second paragraph). Therefore, since intraventricular injection of methotrexate as taught by Chamberlain et al. (1998) would result in only a small amount of circulation of the injected drug, via the cerebrospinal fluid, into the spinal cord, the concentration of methotrexate achieved would not be expected by one of skill in the art to be as high as could be achieved through direct administration into the spinal cord area via intrathecal

administration. The subarachnoid space, as shown in Figure 12.20 on page 404 of the text cited above, is not the area touched through intrathecal administration. Most importantly, contrary to the Examiner's suggestion, one of skill would understand that intraventricular administration leading to subdural circulation is referring to the subdural area of the brain NOT the spinal cord. This is again a basic anatomical feature that allows for separation of the brain and spinal cord areas in the body. Thus, this fact, combined with the fact that nowhere does the cited reference teach or suggest use of methotrexate intrathecally at any dose for relief of pain indicates that this reference does not teach or suggest the method of the instant invention. It is critical that the Examiner understand that the concentration of drug achieved at the local site, in the spinal cord, must be high enough to produce a pharmacological effect, without producing unwanted side effects. This is another basic tenet of pharmacology; dose-response dictates whether a drug is effective and safe. Such a pharmacological action, with safety, is only achieved by intrathecally administering the drug, NOT by giving the drug into the brain's ventricular system as the Examiner suggests.

In order to establish a *prima facie* case of case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly the reference cited fails to teach or suggest the invention as originally claimed. However, in an earnest effort to advance the prosecution of this case, Applicants have further amended claim 1 to recite that the methotrexate dose is a dose no lower than 1 mg/kg and less than 3 mg/kg. This dose range does not overlap the dose range taught by the cited reference. The reference cited, in fact, teaches a much lower dose range and a different route of administration. Therefore, this reference fails to teach the limitations of the claim as amended and also fails to provide one of skill with an expectation of success. It is only with the specification in hand that one of skill would understand that intrathecal administration at that particular dose level would be effective for treating radiculopathy. Accordingly, this reference cannot

make obvious the invention of the amended claim. Withdrawal of this rejection is respectfully requested.

II. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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